12. (Added) The method of claim 11, further comprising contacting antibodies from the patient with a polypeptide selected from an HMG-1 family, or an effective fragment thereof, wherein the polypeptide or fragment reacts with an antibody to HMG-1.

13. (Added) The method of claim 11, further comprising determining whether the patient is ANCA-negative or ANCA-positive.--

REMARKS

Of original claims 1-9, claims 4, 6-7, and 9 are amended. Claims 1-3, 5, and 8 have been cancelled. Independent claims 10-11 have been added. Dependent claims 12-13 have been added. With this response, claims 4, 6-7, and 9-13 are now pending. Enclosed is a check containing the large entity fee of $80 for the net addition of one independent claim. If the check is missing or insufficient, the Commissioner is authorized to deduct the fees from Baker Botts L.L.P. Deposit Account No. 02-0383.

Added claim 10 is directed towards a method of diagnosing autoimmune diseases in a patient by detecting the presence or absence of antibodies in the patient to HMG-1, HMG-2, or both HMG-1 and HMG-2, and diagnosing the autoimmune disease based on the antibodies detected. Added claims 11- 13 are directed towards methods of diagnosing the cause or prognosis of an ulcerative colitis patient comprising contacting antibodies from the patient with a polypeptide selected from an HMG-2 family, and optionally an HMG-1 family, to confirm the cause and prognosis of the disease. Support for the new claims may be found throughout the specification, for example, at page 23, lines 21-32; and page 34, line 8-page 38, line 6 (presence of anti-HMG-2 antibody in serum varies with ANCA status, refractory nature of disease, and type of colitis).

For the Examiner's convenience, a list of currently pending claims is attached at the end of this document.

I. Sequence listing

Applicant has enclosed a paper copy and computer readable version of the sequence listing. Both the paper copy and computer readable version contain the same biological sequences.

II. Rejection under 35 U.S.C. § 102(b)

Claims 1-3 and 7-9 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ayer et al. (*Arthritis & Rheumatism* 37(1): 98-103 (1994); hereinafter "Ayer").

For a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference. *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677, 7 U.S.P.Q.2d 1315, 1317 (Fed. Cir. 1988).

Ayer described the testing of patients for HMG autoantibodies after they were treated with procainamide or other drugs. Immunoblotting and ELISA were used to detect the antibodies. The drugs were used to induce lupus in patients.

The Examiner stated that Figure 1 of Ayer discloses bovine HMG-1 and HMG-2 proteins, and that Figure 3 of Ayer shows the use of the proteins in the detection of autoantibodies to systemic lupus erythematosus (SLE).

Applicant has canceled claims 1-3, 5, and 8, and amended claims 4 and 7 in order to expedite prosecution. As amended, claims 4 and 6 are directed towards kits useful for diagnosing a number of autoimmune diseases (*e.g.*, human systemic lupus erythematosus, Sjögren's syndrome, Behçet's disease, scleroderma, primary biliary cirrhosis, microscopic polyangitis/polyarteritis nodosa, ulcerative colitis, Chrohn's disease, and autoimmune hepatitis).

The kits comprise a first HMG-1 antigen, a second HMG-2 antigen, components for detecting the presence of antigen-antibody complexes, and a protocol for correlating the detection of the antigen-antibody complexes with an autoimmune disease. Claims 7 and 9 are directed towards methods for diagnosing autoimmune diseases by detecting antibodies to HMG-1, HMG-2, or fragments thereof.

Applicant asserts that the instant invention differs from the suggestions of Ayer in at least two significant concepts. First, Ayer discusses the concentrations of antibodies in drug-induced diseases, rather than in naturally occurring diseases. Second, Ayer suggests a high correlation between anti- HMG-14 and HMG-17 levels and drug-induced autoimmunity, but not between anti- HMG-1 and HMG-2 levels and drug-induced autoimmunity. HMG-1,2 enzymes are quite distinct from HMG-14,17 enzymes.

Ayer reported a study of the prevalence of autoantibodies to HMG proteins in individuals with drug-induced lupus (DIL), not naturally occurring Systemic Lupus Erythematosus (SLE). Results of the Ayer study showed that 67% of individuals with drug-induced lupus bound HMG-14 and /or HMG-17, whereas only 21% bound HMG-1 and/or HMG-2 (Ayer, Abstract and page 102, col. 1). In other words, Ayer found a significant increase in antibodies to HMG-14 and /or HMG-17, rather than to HMG-1 and HMG-2, in a majority of patients. SLE and drug-induced lupus are not identical, and lead to different antibody characteristics and concentrations (see Clayton et al., *Clin. Exp. Immunol.* 56: 263-271 (1984) and Yung et al., *Arthritis and Rheumatism* 40(7): 1334-1343 (1997); copies enclosed).

HMG-14 and HMG-17 enzymes are quite distinct from HMG-1 and HMG-2 enzymes. The amino acid sequences of HMG-14 and HMG-17 are as follows.

Human HMG-14 (Accession number NP_004956; 100 amino acids)

MPKRKVSSAE GAAKEEPKRR SARLSAKPPA KVEAKPKKAA AKDKSSDKKV
QTKGKRGAKG KQAEVANQET KEDLPAENGE TKTEESPASD EAGEKEAKSD

Human HMG-17(Accession number NP_005508; 90 amino acids)

MPKRKAEGDA KGDKAKVKDE PQRRSARLSA KPAPPKPEPK PKKAPAKKGE
KVPKGKKGKA DAGKEGNNPA ENGDAKTDQA QKAEGAGDAK

Human HMG-1 and HMG-2 (SEQ ID NOS:1-2, respectively) are significantly larger proteins (214 and 208 amino acids, respectively) than are HMG-14 and HMG-17. Applicant asserts that HMG-1 and HMG-2 are significantly different from HMG-14 and HMG-17, and request that the Examiner provide evidence of their similarity which would lead one of skill in the art to consider them equivalent. One of skill in the art would not expect that antibodies against HMG-14 and HMG-17 would be at all related to antibodies against HMG-1 and HMG-2.

Although Ayer reports immunoblotting using HMG-1 and HMG-2, as well as other HMG-proteins, Ayer appears to suggest against the detection of antibodies against HMG-1 and HMG-2 as a diagnostic to detect drug-induced lupus in humans. Ayer's suggestion that levels of antibodies to HMG-14 and HMG-17 increased, while those to HMG-1 and HMG-2 did not would lead one of skill in the art to look away from anti- HMG-1 and HMG-2 antibodies as a predictive tool.

In addition, although Ayer mentions studies finding antibodies to HMG-1 and HMG-2 in a minority of patients with juvenile rheumatoid arthritis and a minority of dogs with SLE (Ayer, page 102, col. 1), Ayer does not disclose or suggest that antibodies against HMG-1 and HMG-2 are associated with any of the specific immune mediated diseases recited in pending claims 4 and 7.

Furthermore, Ayer does not disclose a kit for diagnosing the autoimmune diseases recited in claim 4 comprising a first HMG-1 antigen, a second HMG-2 antigen, a first component for detecting the presence of a first antigen-antibody complex, a second component for detecting the presence of a second antigen-antibody complex, and a protocol for correlating the results with the autoimmune diseases listed in claim 4. In addition, Ayer does not disclose a method for diagnosing the autoimmune diseases recited in claim 7 using HMG-1 and HMG-2 antigens to detect antibodies in the patient.

Neuer et al. (*Arthritis and Rheumatism*, 35(4): 472-475 (1992); copy enclosed) states that antibodies against HMG-1 or HMG-2 are not useful in the prediction of juvenile rheumatoid arthritis. Antibodies against HMG-17 (and not against HMG-14) were found to be of serologic value (pages 474-475). This reference would lead a skilled artisan to look away from HMG-1 and HMG-2 as tools for the diagnosis of the autoimmune diseases recited in the pending claims.

As Ayer does not teach an association between antibodies against HMG-1 or HMG-2 and human systemic lupus erythematosus, Sjögren's syndrome, Behçet's disease, scleroderma, primary biliary cirrhosis, microscopic polyangitis/polyarteritis nodosa, ulcerative colitis, Chrohn's disease and autoimmune hepatitis, it cannot be said to anticipate claims 4, 6-7, and 9.

Applicants respectfully request that the rejections of claims 4, 6-7, and 9 under 35 U.S.C. § 102 be withdrawn.

III. Rejection under 35 U.S.C. § 103

Claims 4-6 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Ayer.

The Examiner asserted that the cited reference and the claimed invention differ only by the placing of HMG-1 or HMG-2 proteins in a kit.

As noted in the previous section, Ayer does not disclose or suggest kits for diagnosing the autoimmune diseases recited in claim 4 (human systemic lupus erythematosus, Sjögren's syndrome, Behçet's disease, scleroderma, primary biliary cirrhosis, microscopic polyangitis/polyarteritis nodosa, ulcerative colitis, Chrohn's disease, and autoimmune hepatitis) by detecting patient antibodies to HMG-1 and HMG-2, nor does it disclose or suggest all of the elements of the kits of claims 4-6. As Ayer does not disclose or suggest all the features of the claimed invention, it cannot be said to make obvious Applicant's invention.

Also, as discussed above, Ayer does not teach the predictive value of anti- HMG-1 and HMG-2 antibodies as predictive tools for diagnosing the indicated diseases. It would not be obvious to one of skill in the art to combine the claimed kit elements.

Claim 5 has been cancelled with this response. Accordingly, applicants request that the rejections of claims 4 and 6 under 35 U.S.C. § 103 be withdrawn.

The Examiner is encouraged to call the undersigned should any further action be required for allowance.

Respectfully submitted,

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Currently pending claims for U.S. Patent Application Serial No. 09/214,881

4. (Amended) A kit for diagnosing an autoimmune disease, the kit comprising:

a first antigen comprising a polypeptide from an HMG-1 family or a fragment of a polypeptide from the HMG-1 family;

a second antigen comprising a polypeptide from an HMG-2 family or a fragment of a polypeptide from the HMG-2 family;

a first component for detecting a first antigen-antibody complex;

a second component for detecting a second antigen-antibody complex; and

an instruction protocol for correlating the detection of either or both of the first antigen-antibody complex and the second antigen-antibody complex with the autoimmune disease, wherein the autoimmune disease is selected from the group consisting of human systemic lupus erythematosus, Sjögren's syndrome, Behçet's disease, scleroderma, primary biliary cirrhosis, microscopic polyangitis/polyarteritis nodosa, ulcerative colitis, Chrohn's disease and autoimmune hepatitis.

6. (Amended) The kit of claim 4, wherein:

the polypeptide from an HMG-1 family is selected from human, bovine, porcine, chicken, mouse, or rat HMG-1; and

the polypeptide from an HMG-2 family is selected from human, bovine, porcine, chicken, mouse, or rat HMG-2.

7. (Amended) A method for diagnosing an autoimmune disease in a patient, the method comprising the step of detecting one or more antibodies in the patient by contacting a reagent with antibodies from the patient, the reagent comprising at least one polypeptide selected from the group consisting of a polypeptide from an HMG-1 family, a polypeptide from an HMG-2 family, and a fragment of a polypeptide from the HMG-1 family or the HMG-2 family, wherein

the at least one polypeptide reacts with an antibody of an autoimmune disease patient, and

the autoimmune disease is selected from the group consisting of human systemic lupus erythematosus, Sjögren's syndrome, Behçet's disease, scleroderma, primary biliary cirrhosis, microscopic polyangitis/polyarteritis nodosa, ulcerative colitis, Chrohn's disease and autoimmune hepatitis.

9. (Amended) The method of claim 7, wherein:

the polypeptide from an HMG-1 family is human, bovine, porcine, chicken, mouse, or rat HMG-1; and

the polypeptide from an HMG-2 family is human, bovine, porcine, chicken, mouse, or rat HMG-2.

10. (Added) A method of diagnosing an autoimmune disease in a patient, the method comprising:

detecting the presence or absence in the patient of antibodies to HMG-1, HMG-2, or both HMG-1 and HMG-2; and

diagnosing the autoimmune disease based on the antibodies detected, wherein the autoimmune disease is selected from the group consisting of human systemic lupus erythematosus, Sjögren's syndrome, Behçet's disease, scleroderma, primary biliary cirrhosis, microscopic polyangitis/polyarteritis nodosa, ulcerative colitis, Chrohn's disease, and autoimmune hepatitis.

11. (Added) A method of diagnosing the cause or prognosis of an ulcerative colitis patient, the method comprising contacting antibodies isolated from the patient with a polypeptide selected from an HMG-2 family, or an effective fragment thereof, wherein the polypeptide or fragment reacts with an antibody to HMG-2.

12. (Added) The method of claim 11, further comprising contacting antibodies from the patient with a polypeptide selected from an HMG-1 family, or an effective fragment thereof, wherein the polypeptide or fragment reacts with an antibody to HMG-1.

13. (Added) The method of claim 11, further comprising determining whether the patient is ANCA-negative or ANCA-positive.